

## Appointment

---

**From:** Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]  
**Sent:** 11/3/2015 12:51:05 PM  
**To:** Jones, Jim [Jones.Jim@epa.gov]  
**Subject:** Accepted: Glyphosate human health meeting  
**Location:** DCRoomRRB41213/ORD; call in Ex. 6 Personal Privacy (PP)  
**Start:** 11/5/2015 8:30:00 PM  
**End:** 11/5/2015 9:30:00 PM  
**Show Time As:** Busy

Message

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**From:** Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]  
**Sent:** 4/6/2015 4:44:43 PM  
**To:** Jordan, William [Jordan.William@epa.gov]  
**Subject:** RE: Three follow up glyphosate questions  
  
**Importance:** High

Hi Bill  
My comment...on the last line

## Ex. 5 Deliberative Process (DP)

JR  
Jess Rowland,  
Deputy Director  
Health Effects Division  
703-308-2719

---

**From:** Jordan, William  
**Sent:** Monday, April 06, 2015 11:54 AM  
**To:** Rowland, Jess  
**Subject:** FW: Three follow up glyphosate questions  
**Importance:** High

Jess —

Based on our phone conversation, here is how I propose to answer the latest question from Mr. Boffey. Please edit it to make it better:

Did you deal with that odd matter where the IARC seems to have decided that EPA's 1991 report did show significant increases in cancer in laboratory animals contrary to the agency's analysis at the time. They refer to an EPA Scientific Advisory Report which apparently said the results were significant using two statistical tests that IARC recommends.

## Ex. 5 Deliberative Process (DP)

Thanks,

Bill

William Jordan  
Deputy Director, Programs  
Office of Pesticide Programs  
U. S. Environmental Protection Agency

Phone: 703-305-1049  
Fax: 703-308-4776

Mailing Address:	Courier Address:
USEPA Headquarters	Potomac Yards South
Clinton Building	2777 Crystal Drive
1200 Pennsylvania Ave., NW	Room 12-235
Mail Code (7501P)	Arlington, VA
Washington, DC 20460	

**From:** Boffey, Philip [<mailto:phboff@nytimes.com>]  
**Sent:** Friday, April 03, 2015 3:24 PM  
**To:** Jordan, William  
**Cc:** Milbourn, Cathy; Daguillard, Robert  
**Subject:** Re: Three follow up glyphosate questions

Sooner is always better.

Did you deal with that odd matter where the IARC seems to have decided that EPA's 1991 report did show significant increases in cancer in laboratory animals contrary to the agency's analysis at the time. They refer to an EPA Scientific Advisory Report which apparently said the results were significant using two statistical tests that IARC recommends.

On Fri, Apr 3, 2015 at 3:12 PM, Jordan, William <[Jordan.William@epa.gov](mailto:Jordan.William@epa.gov)> wrote:

Thanks. Ex. 6 Personal Privacy (PP)

I have put our answers into the clearance process. They should definitely be to you by Monday, but Robert or Cathy may be able to send them sooner.

Have a good weekend.

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

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Fax: 703-308-4776

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USEPA Headquarters

Potomac Yards South

Clinton Building

2777 Crystal Drive

1200 Pennsylvania Ave., NW

Room 12-235

Mail Code (7501P)

Arlington, VA

Washington, DC 20460

**From:** Boffey, Philip [mailto:[phboff@nytimes.com](mailto:phboff@nytimes.com)]

**Sent:** Friday, April 03, 2015 3:05 PM

**To:** Jordan, William

**Cc:** Milbourn, Cathy; Daguiard, Robert

**Subject:** Re: Three follow up glyphosate questions

Hi Bill,

My editorial on glyphosate has been postponed until next week so I don't need your answers until Monday. No harm in sending something earlier but the pressure is off if you're feeling lousy or have hit a stumbling block.

Phil

On Fri, Apr 3, 2015 at 7:36 AM, Philip Boffey <[phboff@nytimes.com](mailto:phboff@nytimes.com)> wrote:

Great. Thanks. Hope it's not too painful.

Sent from my iPhone

On Apr 3, 2015, at 7:30 AM, "Jordan, William" <[Jordan.William@epa.gov](mailto:Jordan.William@epa.gov)> wrote:

**Ex. 6 Personal Privacy (PP)** but I will try to send answers before noon.

Thanks

Bill

Sent from my Windows Phone

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**From:** Philip Boffey  
**Sent:** 4/2/2015 9:33 PM  
**To:** Jordan, William  
**Cc:** Milbourn, Cathy  
**Subject:** Three follow up glyphosate questions

Hi Bill,

In looking more closely at the Lancet Oncology summary and a two-page IARC summary issued the same day (March 20), I see they say there is convincing evidence that glyphosate can cause cancer in laboratory animals as well as DNA or chromosomal damage in human and animal cells. One study of residents in several communities where glyphosate was sprayed found increases in blood markers for chromosomal damages.

1) Was EPA aware of these studies? Did you also conclude there was nothing in them that would change your 1991 conclusions, as you did with the 55 epidemiological studies?

2) Would I be out on a limb to declare on my own authority (not attributed to the agency) that it seems unlikely EPA will change its 1991 judgment that glyphosate is probably not a human carcinogen?

3) An editor asks whether overuse of glyphosate has led to widespread emergence of glyphosate-resistant weeds. Is that an issue that EPA considers in regulating pesticides?

An answer tomorrow morning would be greatly appreciated.

Phil Boffey

Sent from my iPad

--

Philip M. Boffey

Editorial Writer

The New York Times

620 Eighth Avenue

New York, N.Y. 10018

Phone: (212) 556-4485

Fax: (212) 556-3815

Email: phboff@nytimes.com

--

Philip M. Boffey

Editorial Writer

The New York Times

620 Eighth Avenue

New York, N.Y. 10018

Phone: (212) 556-4485

Fax: (212) 556-3815

Email: phboff@nytimes.com

Message

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**From:** Rowland, Jess [Rowland.Jess@epa.gov]  
**Sent:** 9/30/2015 4:23:18 PM  
**To:** Housenger, Jack [Housenger.Jack@epa.gov]  
**Subject:** RE: can we

Yes; except on October 9th, Friday. I am off

Sent from my Windows Phone

---

**From:** Housenger, Jack  
**Sent:** 9/30/2015 11:47 AM  
**To:** Vogel, Dana; Rowland, Jess  
**Subject:** can we

Brief Jim soon on the glyphosate cancer call?

Jack E. Housenger, Director  
Office of Pesticide Programs  
703-308-8163

Message

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**From:** Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]  
**Sent:** 11/20/2015 7:52:12 PM  
**To:** Vogel, Dana [Vogel.Dana@epa.gov]  
**CC:** housenger.jack@epa.gov  
**Subject:** RE: Glyphosate questions

DV

I am working on a response to the 2 questions as we speak.  
Will send it to you, Jack and Jordan later today or tomorrow.  
Did u ask Jack about Timmy Twitching !!!!!

JR  
Jess Rowland,  
Deputy Director  
Health Effects Division  
703-308-2719

-----Original Message-----

From: Vogel, Dana  
Sent: Friday, November 20, 2015 2:50 PM  
To: Rowland, Jess <Rowland.Jess@epa.gov>  
Subject: Glyphosate questions

Jr  
Had the general with Jack. He asked about answers to these questions; Cancer guidelines causation v association as well as pair wise v trends. Also did we do a systematic review? I think the answer to the last q is yes but pls confirm

Dana Vogel  
Sent from my iPhone

Message

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**From:** Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]  
**Sent:** 11/3/2015 12:44:15 PM  
**To:** Nguyen, Khue [Nguyen.Khue@epa.gov]; Moriarty, Thomas [Moriarty.Thomas@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]  
**Subject:** Glyphosate- Web content  
**Attachments:** Glyphosate Web Content 11-2-15 clean after prd comments\_smithedits\_MMP km+JR 11.3.15docx.docx

**Importance:** High

Hi Khue

Here is the document with my edits, especially the cancer and the EDSP sections.  
It has the edits of the others as well

Thanks

JR  
Jess Rowland,  
Deputy Director  
Health Effects Division  
703-308-2719

Message

---

**From:** Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]  
**Sent:** 4/6/2015 4:27:38 PM  
**To:** Jordan, William [Jordan.William@epa.gov]  
**CC:** housenger.jack@epa.gov; Vogel, Dana [Vogel.Dana@epa.gov]  
**Subject:** RE: Three follow up glyphosate questions  
**Attachments:** CPRC II.pdf

**Importance:** High

Hi Bill

Here is our response to Mr. Boffey's inquiry (e-mail below).

With the specific statement:

They refer to an EPA Scientific Advisory Report which apparently said the results were significant using two statistical tests that IARC recommends.

I think they are picking up this from the SAP report line ".....nevertheless, the occurrence .....highly significant" which I have in the end. This, of course, a typical SAP thing!!!

For details please refer to Pages 13 and 14 of the attached 1991 CARC report. Actually, the SAP did not consider the mouse kidney tumors to be a concern and gave a Group D classification. Here is an abridged version.

Kidney tumors- Male mice.

On February 11, 1985 glyphosate was classified as a **Group C** Chemical; "possible human carcinogen" based on kidney tumors in male mice.

Following this meeting, since kidney tumors are rare in mice, HED requested re-examination of kidney of mice from all groups (controls and all dose levels).

The reexamination revealed the presence of a kidney tumor in one concurrent control mice that was not diagnosed in the initial evaluation. Thus, the incidences were 1/49 controls vs. 3/50 at the high dose (30,000 ppm; 4500 mg/kg/day).

On February 11 & 12, 1986 the FIFRA SAP evaluated the available studies and placed glyphosate as a **Group D** chemical; "**not classifiable as to human carcinogenicity**". The SAP determined that after adjusting for greater survival of the mice at the high dose, compared to concurrent controls, there was no pair-wise statistical significance for the increase at the high dose (3/50; 6%) when compared to controls (1/49 ;2%). The lack of pair-wise significance (which is vital) supersedes the presence of statistical significance when compared to historical control incidences. Historical control data from the testing laboratory between 1978 and 1982 indicated the presence of this type of tumor in 2/19 control groups).

On June 26, 1991, HED's Carcinogenicity Peer Review Committee (CPRC) concluded that the tumors are not biologically significant since: there was no pair-wise significance; no increase in corroborative non-neoplastic renal tubular lesions such as hypertrophy or hyperplasia; re-examination of all the kidneys did not result in additional neoplasms; and the incidences (3 tumor bearing mice) was low considering the high dose (30,000 ppm or 4500 mg/kg/day) which is 4.5 times the Limit Dose (1000 mg/kg/day) that produced highly significant reduction in body weight gain in males.

Pancreatic tumors- Male Rats

The CPRC concluded that the pancreatic islet cell tumor is not treatment-related since: the increase did not show statistical significance; only adenomas (no progression to malignancy); the incidences for the two rat studies did not

show dose response for adenomas or adenoma/carcinomas combined; and the incidences were within the historical control range for this tumor type in male rats.

WOE for Classification: **Group E**; Evidence for non-carcinogenicity for humans

- No evidence for carcinogenicity in female mice and equivocal evidence in males
- No evidence for carcinogenicity in male or female rats
- No evidence for genotoxicity
- No structure-activity concern

Excerpt from the SAP Report

**Panel Response:**

In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal. Only small numbers of tumors were found in any group, including those at the highest dose which appear to have exceeded the maximal tolerated dose. The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum. In addition, the statistical analysis shall be age-adjusted; when this is done, no oncogenic effect of Glyphosate is demonstrated using concurrent controls. Nevertheless, the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant. Furthermore, categorization of the oncogenic risk of Glyphosate is complicated by the fact that doses used in the rat study do not appear to have reached the maximal tolerated dose. Under these circumstances, the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions.

Regarding the issue of using historical or concurrent controls, the Panel believes that this has to be decided on a case-by-case basis. For Glyphosate, the historical control data support that there may be reason for concern. However, the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.

JR  
Jess Rowland,  
Deputy Director  
Health Effects Division  
703-308-2719

---

**From:** Jordan, William  
**Sent:** Friday, April 03, 2015 4:50 PM  
**To:** Rowland, Jess; Miller, David  
**Subject:** RE: Three follow up glyphosate questions

Thanks. If you can look into it on Monday morning, that is soon enough.

Enjoy the day at the museum.

And the lovely weekend too.

Bill

William Jordan  
Deputy Director, Programs  
Office of Pesticide Programs  
U. S. Environmental Protection Agency

Phone: 703-305-1049  
Fax: 703-308-4776

Mailing Address:	Courier Address:
USEPA Headquarters	Potomac Yards South
Clinton Building	2777 Crystal Drive
1200 Pennsylvania Ave., NW	Room 12-235
Mail Code (7501P)	Arlington, VA
Washington, DC 20460	

---

**From:** Rowland, Jess  
**Sent:** Friday, April 03, 2015 4:40 PM  
**To:** Jordan, William; Miller, David  
**Subject:** RE: Three follow up glyphosate questions

I am at the natural museum of history!! As I recall the 1991 report the sap said the statistical significance of the mouse kidneys tumors were actually due to a higher survival at the high dose and therefore it's scewed. I will confirm and send a mail.

oh you have that report too.

Sent from my Windows Phone

---

**From:** Jordan, William  
**Sent:** 4/3/2015 3:26 PM  
**To:** Rowland, Jess; Miller, David  
**Subject:** FW: Three follow up glyphosate questions

Another question from the NYT folks. Again I would appreciate your help.

Thanks,

Bill

William Jordan  
Deputy Director, Programs  
Office of Pesticide Programs  
U. S. Environmental Protection Agency

Phone: 703-305-1049

Fax: 703-308-4776

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**From:** Boffey, Philip [<mailto:phboff@nytimes.com>]

**Sent:** Friday, April 03, 2015 3:24 PM

**To:** Jordan, William

**Cc:** Milbourn, Cathy; Daguiard, Robert

**Subject:** Re: Three follow up glyphosate questions

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On Fri, Apr 3, 2015 at 3:12 PM, Jordan, William <[Jordan.William@epa.gov](mailto:Jordan.William@epa.gov)> wrote:

Thanks. The dentist visit was not bad.

I have put our answers into the clearance process. They should definitely be to you by Monday, but Robert or Cathy may be able to send them sooner.

Have a good weekend.

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

Phone: 703-305-1049

Fax: 703-308-4776

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1200 Pennsylvania Ave., NW

Mail Code (7501P)

Washington, DC 20460

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2777 Crystal Drive

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Arlington, VA

**From:** Boffey, Philip [<mailto:phboff@nytimes.com>]

**Sent:** Friday, April 03, 2015 3:05 PM

**To:** Jordan, William

**Cc:** Milbourn, Cathy; Daguiard, Robert

**Subject:** Re: Three follow up glyphosate questions

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Phil

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Sent from my iPhone

On Apr 3, 2015, at 7:30 AM, "Jordan, William" <[Jordan.William@epa.gov](mailto:Jordan.William@epa.gov)> wrote:

I am at the dentist this morning, but I will try to send answers before noon.

Thanks

Bill

Sent from my Windows Phone

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**From:** Philip Boffey  
**Sent:** 4/2/2015 9:33 PM  
**To:** [Jordan, William](#)  
**Cc:** [Milbourn, Cathy](#)  
**Subject:** Three follow up glyphosate questions

Hi Bill,

In looking more closely at the Lancet Oncology summary and a two-page IARC summary issued the same day (March 20), I see they say there is convincing evidence that glyphosate can cause cancer in laboratory animals as well as DNA or chromosomal damage in human and animal cells. One study of residents in several communities where glyphosate was sprayed found increases in blood markers for chromosomal damages.

1) Was EPA aware of these studies? Did you also conclude there was nothing in them that would change your 1991 conclusions, as you did with the 55 epidemiological studies?

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Sent from my iPad

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Editorial Writer

The New York Times

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Phone: (212) 556-4485

Fax: (212) 556-3815

Email: phboff@nytimes.com

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

008828

OCT 30 1991

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

**MEMORANDUM**

**SUBJECT: SECOND Peer Review of Glyphosate**

CAS No. 1071-83-6  
EPA Chem. Code 417300  
40 CFR 180.364  
TOX Chem. No.: 661A  
Reg Group: List A (6B)

**FROM:** William Dykstra, Ph.D.  
Toxicology Branch I (IRS)  
Health Effects Division (H7509C)

*William Dykstra*

and

George Z. Ghali, Ph.D.  
Science Analysis and Coordination Branch  
Health Effects Division (H7509C)

*G. Ghali 8/22/91*

**TO:** Robert Taylor, PM 25  
Fungicide-Herbicide Branch  
Registration Division (H7505C)

and

Lois Rossi, Chief  
Reregistration Branch  
Special Review and Reregistration Division (H7508W)

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 1991 to discuss and evaluate the weight of the evidence on Glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.



Printed on Recycled Paper

1510

A. Individual in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp

Penelope A. Fenner-Crisp

William L. Burnam

Wm L Burnam

Karl Baetcke

Karl Baetcke

Marcia Van Gemert

Marcia van Gemert

Esther Rinde

E. Rinde

Hugh Pettigrew

Hugh M. Pettigrew

Marion Copley

Marion Copley

Lucas Brennecke

Lucas H. Brennecke

George Ghali

G. Ghali

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signature indicates concurrence with the overall conclusions of the Committee.)

Reto Engler

Reto Engler

Richard Hill

Richard Hill

John Quest

John A. Quest

Kerry Dearfield

Kerry Dearfield

Yin-Tak Woo

Yin Tak Woo

Jean Parker

Jean Parker

NON CONCUR

William Sette

William Sette

Robert Beliles

DO NOT CONCUR

Julie Du

Julie Du

3. Scientific Reviewers (Committee or noncommittee members responsible for data presentation; signature indicates technical accuracy of panel report.)

William Dykstra

William Dykstra

Roger Gardner

Roger Gardner 9-5-91

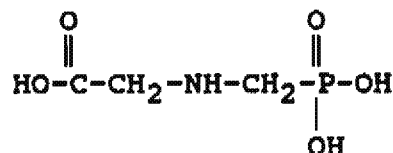
## B. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine, marketed under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a wide spectrum plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. It acts by the inhibition of amino acid synthesis.

Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated March 4, 1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of February 11-12, 1986 (report dated February 24, 1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of

- 4 -

these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study had been evaluated by the Peer Review Committee.

#### C. Material Evaluated

The material available for review consisted of a document prepared by Dr. William Dykstra summarizing major scientific and regulatory issues and relevant toxicology information, data evaluation records of a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice, the FIFRA Scientific Advisory Panel report dated Feb 24, 1986, a review of historical control data on mouse kidney tumors, a toxicology one-liner for the glyphosate data base and an OPP peer review report entitled "Consensus Review of Glyphosate" dated March 4, 1985.

#### D. Evaluation of Carcinogenicity Data

1. Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.

##### a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was conducted at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

##### b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in male rats. Because of the absence of a dose-response relationship, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose

group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not reflect a carcinogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic Lesions and Adequacy of Dosing Considerations

No effect of treatment on the incidence of nonneoplastic lesions was noted. No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was adequate to evaluate the carcinogenic potential of glyphosate.

2. Stout, L. D. and Ruecker, F. A. (1990). Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; Sept. 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.

a. Experimental Design

This chronic toxicity/carcinogenicity study in the rat was submitted to the Agency as a replacement study for the 26-month 1981 chronic toxicity/carcinogenicity study in the rat. In this study, randomized groups of 60 male and 60 female young (8 weeks old) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, or 20,000 ppm or the equivalent of 0, 100, 400, and 1000 mg/kg/day of technical glyphosate for 2 years. At 12 months, 10 animals/sex/group were sacrificed.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data are presented. The most frequently observed tumors in this study were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. The following is a discussion of each type of tumor.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates\* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values).

<u>Tumors</u>	<u>Dose (ppm)</u>			
	<u>0</u>	<u>2000</u>	<u>8000</u>	<u>20,000</u>
Carcinomas	1/43 <sup>a</sup>	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48 <sup>b</sup>
(%)	(2)	(18)	(10)	(15)
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48 <sup>c</sup>
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236	0.526	0.649

- \* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.  
<sup>a</sup> First carcinoma observed at week 105, dose 0 ppm.  
<sup>b</sup> First adenoma observed at week 81, dose 20000 ppm.  
<sup>c</sup> First hyperplasia observed at week 91, dose 20000 ppm.  
<sup>d</sup> p ≤ 0.05; Fisher's Exact test with Bonferoni correction.

## Note:

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then p < 0.05.

Historical control data on the incidence of pancreatic islet cell adenomas from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	No. Affected	% Affected
1	07/83	24	68	2	2.9
2	02/85	23	59	5	8.5
3	10/85	24	69	4	5.8
4	06/85	24	57	1	1.8
5	09/88	24	60	5	8.3
6	01/89	24	60	3	5.0
7	03/89	24	59	3	5.1

Committee's interpretation: Although the incidences of the pancreatic islet cell adenomas at the low-, mid- and high-dose groups exceeded the historical control range of 1.8 to 8.5 percent in male rats, there was no statistically significant positive dose-related trend in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia was not dose-related. Therefore, the pancreatic islet cell tumors were not considered to be compound-related. It was also noted that the incidence of this lesion in the concurrent control for males was at the low end of the historical control range. The Committee concluded that the apparent statistical significance of the pairwise comparisons of the treated male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response.

The incidences of islet cell pancreatic tumors in the earlier rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day)			
	0	3	10	30
Hyperplasia (%)	3/50 (6)	2/49 (4)	1/50 (2)	0/50 (0)
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Adenoma/carcinoma (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5. Historical control ranges for the thyroid tumors in Sprague-Dawley rats were reported as shown in Table 6.

Committee's interpretation: Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

- 9 -

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm)			
	0	2000	8000	20,000
Carcinomas	0/54	2/55 <sup>a</sup>	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54 <sup>b</sup>	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p =	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5/58 <sup>c</sup>	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601

<sup>a</sup> First carcinoma observed at week 93 at 8000 ppm.

<sup>b</sup> First adenoma observed at week 54 at 0 ppm.

<sup>c</sup> First hyperplasia observed at week 54 at 8000 ppm.

<sup>\*</sup> Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then  $p < 0.05$ .

- 10 -

Table 5: Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates\* and Cochran-Armitage Trend Test and Fisher's Exact Tests Results (p values).

Tumors	Dose (ppm)			
	0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59 <sup>a</sup>	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59 <sup>b</sup>	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031 <sup>*</sup>	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033 <sup>*</sup>	0.671(n)	0.090	0.124
Hyperplasia only	10/57 <sup>c</sup>	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)

<sup>a</sup> First carcinoma observed at week 93 at 8000 ppm.

<sup>b</sup> First adenoma observed at week 72 at 0 ppm.

<sup>c</sup> First hyperplasia observed at week 54 at 8000 ppm.

<sup>\*</sup> Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then  $p < 0.05$ .

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%)	
	Males	Females
Carcinomas	0.0 - 5.2	0.0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10.0
Hyperplasia	4.3 - 20.0	4.3 - 16.9

iii. Liver (Table 7)

There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

- 12 -

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm)			
	0	2000	8000	20,000
Carcinomas (%) p =	3/44 (7) 0.324	2/45 (4) 0.489 (n)	1/49 (2) 0.269 (n)	2/48 <sup>a</sup> (4) 0.458 (n)
Adenomas (%) p =	2/44 (5) 0.016	2/45 (4) 0.683 (n)	3/49 (6) 0.551	7/48 <sup>b</sup> (15) 0.101
Adenoma/carcinoma (%) p =	5/44 (11) 0.073	4/45 (9) 0.486 (n)	4/49 (8) 0.431 (n)	9/48 (19) 0.245
Hyperplasia only (%) p =	0/44 (0) 0.462	0/45 (0) 1.000	1/49 <sup>c</sup> (2) 0.527	0/48 (0) 1.000

<sup>a</sup> First carcinoma observed at week 85 at 20,000 ppm.

<sup>b</sup> First adenoma observed at week 88 at 20,000 ppm.

<sup>c</sup> First hyperplasia observed at week 89 at 8000 ppm.

<sup>\*</sup> Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then  $p < 0.05$ .

Committee's interpretation: Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

- 13 -

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogenicity testing in rats. However, it appears that animals could have tolerated higher doses.

3. Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamics Inc., dated July 21, 1983. Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.

a. Experimental Design

Groups of 50 male and 50 female CD-1 mice were administered glyphosate in the diet at concentrations of 1000, 5000, or 30,000 ppm for 18 months.

b. Discussion of Tumor Data

Glyphosate produced an equivocal carcinogenic response in males characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee, in their meeting of February 11, 1985, tentatively classified glyphosate as a "Class C" carcinogen (report dated March 4, 1985). The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (the incidence in the control group was originally reported as 0/49 before the reexamination of the slides).

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

- 14 -

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert assistance of the FIFRA Scientific Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP, in their meeting of February 11-12, 1986, proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

Committee's interpretation: In their meeting of June 26, 1991, the Health Effects Carcinogenicity Peer Review Committee concluded that despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females.

- 15 -

c. Nonneoplastic lesions:

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Glyphosate was tested in this study at levels higher than the limit dose. Body weight gain in males of the high dose was 13, 17 and 27% less than the controls at 3, 12 and 24 months respectively. The decrease in body weight gains was statistically significant ( $p < 0.01$ ). This effect was less obvious in females. The doses tested were considered adequate for the carcinogenic potential assessment of glyphosate.

E. Additional Toxicology Data on Glyphosate

1. Metabolism

When Sprague-Dawley rats were given a single oral dose of C-14 glyphosate, 30 to 36 percent of orally administered glyphosate was absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO<sub>2</sub> within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Amino methyl phosphonic acid (AMPA) was found in the excreta of animals at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate found.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate

- 16 -

does not significantly change the metabolism, distribution, or excretion of glyphosate.

#### N-Nitrosoglyphosate (NNG)

The Agency has determined that carcinogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm [see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"]. The levels of NNG in technical glyphosate have been examined by HED. The overall NNG content in individual samples of technical glyphosate analyzed at production plants is shown below:

<u>Samples Analyzed</u>		<u>NNG Observed</u>
<u>No. Samples</u>	<u>Per cent</u>	<u>(ppb)</u>
2035	92.6	< 1000
124	5.6	1000 - 1500
24	1.1	1500 - 2000
13	0.6	2000 - 3000
2	0.1	> 3000

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

## 2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Salmonella assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells in vitro both with and without S-9 up to toxic levels (10 mg/mL) and rec assay with B. subtilis up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 0.0000135 and 0.125 mg/ml, and a dominant lethal assay in mice up to 2000 mg/kg.

## 3. Developmental and Reproductive Toxicity

In rats, doses up to 3500 mg/kg/day showed no evidence of malformations. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain

- 17 -

deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

In rabbits, doses up to 350 mg/kg/day showed no evidence of malformations. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In a three-generation reproduction study in the rat, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F<sub>3b</sub> generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

#### 4. Structure - Activity Relationships

Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and reported to be negative.

#### 5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate is not considered to be toxic to mammals (rat oral LD<sub>50</sub> of 4320 mg/kg (both sexes), and a dermal LD<sub>50</sub> greater than 7940 mg/kg in rabbits).

A 1-year chronic feeding study in dogs at 6/sex/dose was conducted using doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

#### F. Weight of the Evidence Considerations

The Committee considered the following findings to be of significance regarding the weight-of-the-evidence determination of the carcinogenic potential of glyphosate.

1. Glyphosate was associated with increased incidences of pancreatic islet cell adenomas in male Sprague-Dawley rats at all treatment levels in comparison to the concurrent control group (Table 1). Although the low- (18%), mid- (10%) and high-dose group (15%) incidences exceeded the 1.8 to 8.5% range of historical controls from Monsanto's EHL data base, the pancreatic islet cell adenomas were not considered

compound-related for the following reasons: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20000 ppm), and b) there was no progression to carcinoma. Tertiary evidence from the open literature cited by the registrant showed a range of 0 to 17% for pancreatic islet cell adenomas in Sprague-Dawley male rats for unadjusted data. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

No increased incidence of these tumors was observed in female rats in comparison to concurrent controls.

2. C-cell adenomas were slightly increased in male and female mid- and high-dose groups in the rat (Tables 4 and 5). Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

3. There was a slight dose-related increase in hepatocellular adenomas in male rats (Table 7), but the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose-related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

4. Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

- 19 -

Despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

5. Glyphosate was tested up to the limit dose in the rat, and up to levels higher than the limit dose in mice.

6. There was no evidence of genotoxicity for glyphosate.

7. Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and was reported to be negative.

G. Classification:

Considering criteria contained in EPA Guidelines (FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based on lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

**END**